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Prognostic Value of Cardiac Troponin T After Noncardiac Surgery: 6-Month Follow-Up Data

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Objectives. **We sought to evaluate the prognostic significance of cardiac troponin T (TnT) serum levels after noncardiac surgery.**

Background. **Cardiac TnT has been found to be a marker for myocardial injury, but elevations of TnT are common in patients undergoing noncardiac surgery without clinical evidence of severe ischemia.**

Methods. **We studied 772 patients who underwent major noncardiac procedures and did not have major cardiovascular complications during their inpatient course. Total serum creatine kinase (CK) and cardiac TnT were measured according to a protocol that included sampling in the recovery room and during the next 2 days. A 6-month follow-up interview was performed for 722 (94%) of the patients.**

Results. **Elevated cardiac TnT and CK-MB results were detected for 92 (12%) and 211 (27%) patients, respectively. During the follow-up period, there were 19 (2.5%) major cardiac complications, including 14 cardiac deaths, 3 nonfatal myocardial infarctions and 2 admissions for unstable angina. Compared with patients with cardiac TnT values <0.1 ng/ml, patients with elevated TnT had a relative risk for cardiac events of 5.4 (95% confidence interval: 2.2 to 13, p = 0.001), whereas CK-MB was not correlated with postdischarge cardiac events. In multivariate logistic regression analysis adjusting for preoperative clinical and CK-MB data, a cardiac TnT value >0.1 ng/ml was an independent correlate of cardiac events (adjusted odds ratio 4.6, p < 0.05). This correlation was a function of the relation of elevated TnT levels with postoperative in-hospital congestive heart failure and new sustained arrhythmias, suggesting that elevated postoperative TnT levels detected myocardial ischemia during these clinical events.**

Conclusions. **We conclude that an abnormal TnT level in patients undergoing noncardiac surgery may be a useful marker of ischemic disease and a predictor of 6-month prognosis.**

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Detection of myocardial injury after noncardiac surgery is complicated by the high prevalence of electrocardiographic (ECG) abnormalities (1) and the high false positive rate of creatine kinase (CK)-MB (2) in this setting. Some data have suggested that newer markers of myocardial injury, including cardiac troponin I (3) and T (4,5), might improve management of patients by identifying those who were having or were at risk for cardiac complications. We (6) have reported that, in patients undergoing major noncardiac surgery, cardiac troponin T (TnT) has a high sensitivity for acute myocardial infarction and, among patients without infarction, has a higher correlation with other cardiac complications than does CK-MB. However, in that cohort, many patients without clinical complications had elevated cardiac TnT values, raising the question of whether these values were false positive results or evidence of subclinical myocardial injury.

To address this issue, we have collected 6-month follow-up data including cardiac outcomes on a subcohort of patients from this previous investigation. The results have implications for the use and interpretation of serum markers after noncardiac surgery.

Methods

Patients. All patients aged ≥50 years who underwent major noncardiac procedures at Brigham and Women's Hospital from December 5, 1991 to May 31, 1994 were eligible for the study. Major noncardiac procedures were defined as those with an expected length of stay ≥2 days. The clinical and cardiac marker data collection protocol is described in a previous report (6) and was approved by the Brigham and Women's Hospital Human Research Committee.

In brief, patients who provided signed informed consent to the full study protocol underwent a preoperative history and

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Abbreviations and Acronyms

CK = creatine kinase
CK-MB = creatine kinase, MB isoenzyme
ECG = electrocardiogram, electrocardiographic
OR = odds ratio
PTCA = percutaneous transluminal coronary angioplasty
RR = relative risk
TnT = cardiac troponin T

physical examination by study personnel using a structured data form. The protocol included postoperative sampling of CK and, if total CK levels were elevated, CK-MB, at the following times: 1) immediately postoperatively in the recovery room, 2) at 8 PM on the evening of the day of operation, and 3) on the next 2 mornings. For patients who could not be approached before the operation for informed consent (22% of the study population), data were included in this report if they underwent postoperative serial cardiac marker sampling (standard practice is measurement of CK and CK-MB every 8 h) and gave informed consent for 6-month follow-up.

Cardiac TnT was measured by using excess serum remaining after performance of CK and CK-MB samples that were ordered either as part of routine care or as part of the study protocol. The mean and median number of cardiac TnT measurements per patient were 3.4 and 3, respectively.

Patients were included in this report only if they had at least two determinations of markers for myocardial injury. Total CK was assayed throughout this study on the ACA discrete clinical analyzer (Du Pont). The upper limits of the reference interval are 218 U/liter and 266 U/liter for women and men, respectively. CK-MB was measured from the beginning of the study to July 30, 1993 with use of a Du Pont ACA ion exchange chromatography and immunoinhibition assay that measures the activity of CK-MB (reference interval 0 to 8 U/liter). Beginning on August 1, 1993, a mass assay for CK-MB, utilizing a monoclonal antibody, was performed on the Stratus instrument (Baxter Diagnostics). The upper limit of the reference interval is 5 ng/ml. Troponin T was measured by an immunoassay procedure that uses complementary monoclonal antibodies (7). Analysis was performed on the ES-300 (Boehringer Mannheim Corporation) and the upper limit of the reference interval is 0.1 ng/ml. The assay is specific for cardiac troponin T (8–12).

The presence or absence of cardiac complications postoperatively was classified by reviewers who used clinical information recorded on structured data forms; these reviewers had no knowledge of cardiac TnT data. The diagnosis of myocardial infarction was made on the basis of CK-MB levels and ECG findings. When the ion exchange chromatography assay was used to assay CK-MB, acute myocardial infarction was diagnosed if 1) the peak CK-MB was >5% of an elevated total CK, or 2) the peak CK-MB was >3% of an elevated total CK in the presence of ECG changes consistent with ischemia or infarction. When the CK-MB mass assay was used, acute myocardial infarction was diagnosed if peak CK-MB levels exceeded the normal range (0 to 5 ng/ml) and the ratio of CK-MB to total CK exceeded 0.0278, a threshold ratio that was estimated to be comparable to a 0.05 threshold with the ion exchange chromatography assay for CK-MB based on the normal ranges for CK-MB with the two assays. If the postoperative ECG had changes consistent with ischemia, acute myocardial infarction was diagnosed if peak CK-MB was elevated and the ratio of CK-MB to total CK exceeded 0.0167.

Major cardiac complications were defined as the occurrence of myocardial infarction or any of the following: 1) pulmonary edema, 2) primary cardiac arrest, 3) ventricular fibrillation, or 4) complete heart block requiring therapeutic intervention to maintain normal hemodynamic function. Criteria for diagnosing pulmonary edema included a blinded interpretation of chest X-ray films by a radiologist. Less severe postoperative cardiac complications that were included in the analysis (congestive heart failure, chest pain with ECG changes and new sustained atrial or ventricular arrhythmia) were defined as present if noted by clinicians in the medical record.

Follow-up data collection. To improve the completeness of follow-up, only residents of Massachusetts were included in this analysis. From the original cohort of 1,177 patients, 34 were excluded because they had major cardiac complications before discharge from the hospital. Of the remaining 1,143 patients, 371 (32%) were excluded because they lived outside Massachusetts. Follow-up by telephone ≥6 months after discharge was performed successfully for 722 (94%) of the remaining 772 patients. A search for death certificates at the Massachusetts Bureau of Vital Statistics was performed for the 6% of patients who could not be contacted.

Nineteen patients were classified as having a postdischarge cardiac complication on the basis of these interviews and review of medical records. In 18 of these 19, the outcome was identified by interview of either the patient or a relative. The outcome of the other patient (a nonfatal myocardial infarction) was identified through medical record review. All 14 patients who were reported during interviews to have died were also recorded as having died in the Massachusetts Registry of Deaths; hence, the absence of a death certificate for the patients who could not be contacted for follow-up can be considered evidence of probable survival.

Specific cause of death was determined through analysis of the death certificates, hospital charts and autopsy reports. The deaths were classified as cardiovascular or noncardiovascular independently by two researchers who had no knowledge of TnT levels. These reviewers agreed in 11 of the 14 cases initially and achieved consensus on the remaining 3 cases after discussion. For patients who were admitted to the hospital postoperatively, medical records were reviewed to determine whether the cause of readmission was acute myocardial infarction, unstable angina or another condition.

Analysis of data. Univariate correlations between clinical characteristics and abnormal TnT and CK-MB levels were calculated by using a chi-square test or a Fisher exact test. Relative risk (RR) for postdischarge cardiac complications was

Table 1. Description of Patients

Characteristic	Cardiac Troponin T Level: Abnormal (n = 92 [100%])	Cardiac Troponin T Level: Normal (n = 680 [100%])	p Value
Age ≥60 yr	82 (89%)	528 (78%)	0.01
Male	70 (76%)	326 (48%)	0.001
White	83 (90%)	633 (93%)	0.32
Diabetic	21 (23%)	86 (13%)	0.008
Hypertension	59 (65%)	296 (44%)	0.001
Current smoking	19 (21%)	123 (18%)	0.04
Hypercholesterolemia	21 (26%)	167 (26%)	0.98
Chest pain presumed to be ischemic	19 (21%)	70 (10%)	0.004
Previous MI	27 (29%)	103 (15%)	0.001
CHF	14 (15%)	41 (6%)	0.001
Prior coronary angiography	28 (32%)	101 (16%)	0.001
Prior CABG	17 (20%)	54 (8%)	0.001
Prior PTCA	1 (1%)	13 (2%)	1.00
Aspirin use	17 (18%)	154 (23%)	0.37
Beta-blocker use	21 (23%)	132 (19%)	0.44
Type of surgery			
General	8 (9%)	138 (20%)	0.008
Gynecologic	0 (0%)	22 (3%)	0.08
Neurologic	1 (1%)	24 (4%)	0.214
Orthopedic	20 (22%)	251 (37%)	0.004
Thoracic	23 (25%)	67 (10%)	0.001
Urologic	10 (11%)	46 (7%)	0.154
Vascular	30 (33%)	132 (19%)	0.004
Postoperative findings			
CHF	11 (12%)	11 (2%)	0.001
Chest pain with ECG changes	1 (1%)	2 (0.3%)	0.3
New arrhythmia	36 (39%)	55 (8%)	0.001
Abnormal CK-MB	62 (67%)	149 (22%)	0.001

CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; CK-MB = creatine kinase MB isoenzyme level; ECG = electrocardiographic; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

calculated for these markers and for other clinical characteristics. Multivariate logistic regression analysis was used to assess the independent correlation of peak cardiac marker levels with postdischarge cardiac complication rates after adjusting for other clinical correlates of complications. Potential confounders considered in these models were variables with univariate correlations with postdischarge complications with a p value <0.2.

Results

Of the 772 patients without postoperative major cardiac complications during their inpatient course, 92 (12%) had elevated (>0.1 ng/ml) cardiac TnT levels postoperatively. Compared with patients who had normal TnT levels, those who had abnormal levels were older and were more likely to be male, to have diabetes or hypertension and to be current smokers of cigarettes (Table 1). Patients with elevated TnT levels were also more likely to report during their preoperative evaluation that they had a history of chest pain, prior myocardial infarction, congestive heart failure, prior coronary angiography and prior coronary artery bypass graft surgery. Abnormal levels of cardiac TnT were significantly less common among patients who underwent orthopedic procedures and were more common among patients who underwent thoracic and vascular procedures. Patients with elevated cardiac TnT were more likely to have elevated peak CK-MB levels postoperatively. Although none of the patients in this cohort had major postoperative cardiac complications, the patients with elevated cardiac troponin T levels had higher rates of postoperative congestive heart failure and new arrhythmias (Table 1). Chest pain with ECG changes was uncommon in patients with or without abnormal cardiac troponin T levels.

Postdischarge course. Of the 772 study subjects, 19 (2.5%) had an adverse postdischarge cardiac outcome during the 6-month follow-up period, including cardiac death in 14, nonfatal myocardial infarction in 3 and admission for unstable angina in 2. Of the patients who had an adverse outcome, 8 (42%) had elevated peak TnT levels, compared with 84 (11%) of the 753 patients without postdischarge complications ($p < 0.05$) (Table 2). Therefore, an abnormal TnT level had a positive predictive value of 8 (9%) of 92 and an RR of 5.4. Abnormal CK-MB values were not significantly correlated with subsequent complications. Other significant ($p < 0.05$) correlates of complications included male gender, history of diabetes, history of ischemic chest pain, congestive heart failure, prior coronary arteriography or revascularization and postoperative congestive heart failure or sustained new arrhythmias.

In stepwise and global multivariate logistic regression analyses that included just preoperative clinical data and CK-MB data, an elevated cardiac TnT level remained an independent predictor of adverse cardiac outcome. In a model adjusting for CK-MB, type of operation, age, gender, previous cardiac history, smoking history, medications and history of diabetes, the adjusted odds ratio (OR) for complications associated with an elevated cardiac TnT level was 4.6 ($p < 0.05$). When data on the occurrence of postoperative congestive heart failure and new sustained arrhythmias were added to multivariate models, cardiac troponin T no longer was a significant independent correlate of postdischarge complications (OR 2.25, $p = 0.32$).

Data presented in Table 3 show that elevated cardiac TnT levels were associated with an increased risk for complications in the low risk subgroups of patients undergoing nonvascular surgery (RR 7.6, $p < 0.001$) and patients without preoperative congestive heart failure (RR 4.1, $p = 0.06$).

Discussion

In this report, we describe 6-month follow-up data for patients who had elevated cardiac TnT levels after noncardiac surgery in the absence of clinical evidence of major cardiac complications. In both univariate analyses and after adjusting for preoperative clinical correlates of complications, cardiac TnT was an independent correlate of complications. This

Table 2. Correlates for Cardiac Complications Within 6 Months After Discharge

Predictor	Patients		RR (95% CI)	p Value
	Total	With Complications		
Cardiac troponin T				
Abnormal*	92	8 (8.7%)	5.4 (2.2–13)	0.001
Normal	680	11 (1.6%)		
CK-MB				
Abnormal*	211	6 (2.8%)	1.2 (0.5–3.2)	0.67
Normal	561	13 (2.3%)		
Age				
≥60 yr	610	17 (2.8%)	2.3 (0.5–9.7)	0.39
<60 yr	162	2 (1.2%)		
Gender				
Male	396	16 (4.0%)	5.1 (1.5–17.2)	0.004
Female	376	3 (0.8%)		
Race				
Nonwhite	56	3 (5.4%)	2.4 (0.7–8.0)	0.15
White	716	16 (2.2%)		
Vascular surgery				
Yes	161	6 (3.7%)	1.8 (0.7–4.5)	0.24
No	611	13 (2.1%)		
Medical history of				
Diabetes				
Yes	107	7 (6.5%)	3.6 (1.5–9.0)	0.003
No	665	12 (1.8%)		
Hypertension				
Yes	355	7 (2.0%)	0.7 (0.3–1.9)	0.52
No	410	11 (2.7%)		
Smoking				
Current	142	4 (2.8%)	1.2 (0.4–3.5)	0.76
Never or past	630	15 (2.4%)		
Hypercholesterolemia				
Yes	188	6 (3.2%)	1.4 (0.5–3.8)	0.46
No	541	12 (2.2%)		
Preoperative history of				
Ischemic chest pain				
Yes	89	6 (6.7%)	3.5 (1.4–9.1)	0.006
No	683	13 (1.9%)		
Myocardial infarction				
Yes	130	6 (4.6%)	2.3 (0.9–5.9)	0.08
No	642	13 (2.0%)		
Congestive heart failure				
Yes	55	10 (18.2%)	14.5 (6.1–34.1)	0.001
No	717	9 (1.3%)		
Prior coronary angiography				
Yes	129	8 (6.2%)	3.4 (1.4–8.3)	0.004
No	607	11 (1.8%)		
Prior CABG				
Yes	71	7 (9.9%)	5.4 (2.2–13.4)	0.001
No	663	12 (1.8%)		
Prior PTCA				
Yes	14	2 (14.3%)	6.0 (1.5–23.7)	0.048
No	719	17 (2.4%)		
Use of aspirin				
Yes	171	6 (3.5%)	1.6 (0.6–4.2)	0.32
No	601	13 (2.2%)		
Use of beta-blocker				
Yes	153	7 (4.6%)	2.4 (0.9–5.9)	0.059
No	619	12 (1.9%)		
Postoperative complications				
Congestive heart failure				
Yes	17	5 (22.7%)	12 (4.1–31)	0.001
No	736	14 (1.9%)		
Chest pain with ECG changes				
Yes	3	0 (0%)	— (—)	1.0
No	750	19 (2.5%)		
New arrhythmia				
Yes	82	9 (9.9%)	6.7 (2.8–16)	0.001
No	671	10 (1.5%)		

*See Methods for definition of abnormal and normal values. CI = confidence interval; RR = relative risk; other abbreviations as in Table 1.

Table 3. Subgroup Analyses: Correlation of Postoperative TnT and CK-MB Levels With Postdischarge Cardiac Complications

Subgroups With Abnormal Serum Markers	RR (95% CI)	p Value
No history of CHF		
TnT	4.1 (1.0–16.1)	0.06
CK-MB	1.3 (0.3–5.3)	0.71
History of CHF		
TnT	2.9 (1.0–8.6)	0.05
CK-MB	1.1 (0.3–3.9)	1.0
Male		
TnT	3.6 (1.4–9.4)	0.005
CK-MB	0.9 (0.3–2.5)	1.0
Female		
TnT	8.0 (0.8–85)	0.17
CK-MB	1.9 (0.2–21)	0.5
Vascular surgery		
TnT	2.2 (0.4–11.4)	0.3
CK-MB	0.8 (0.1–6.2)	1.0
Other surgery		
TnT	7.6 (2.6–21.9)	0.001
CK-MB	1.5 (0.5–4.6)	0.54

TnT = cardiac troponin T; other abbreviations as in Tables 1 and 2.

correlation became nonsignificant when data on postoperative congestive heart failure and new sustained arrhythmias were introduced into multivariate analyses.

These data are consistent with the hypothesis that elevated TnT levels in these patients may reflect degrees of myocardial ischemia that were not sufficient to cause CK-MB abnormalities or to lead to chest pain and ECG abnormalities that were detected through routine clinical care. The findings indicate that postoperative cardiovascular events such as heart failure and arrhythmias may often have an ischemic pathophysiology and that cardiac TnT may enhance identification of high risk patients.

These findings are consistent with and extend previous research on cardiac TnT as a marker of myocardial injury. Other studies (13–17) have shown that, in patients with unstable angina, TnT elevations identify patients with an increased risk for cardiac complications. However, in these studies, many patients with elevated cardiac TnT levels did not have complications. These findings have raised the question of whether longer-term follow-up might also identify these patients with false positive results as having an increased risk for cardiac complications.

Our data must be interpreted in the context of the study design. Detection of clinical complications after the noncardiac operations was dependent on the notes recorded by the responsible physicians as part of routine care. Physicians were not provided with cardiac TnT results, and patients who had elevated TnT levels might have had a higher rate of diagnoses of cardiac complications during their hospital stay had they undergone a more systematic and comprehensive monitoring protocol. In addition, the sampling protocol of TnT and CK-MB may have missed abnormal values that would have led to classification of more patients as having had acute myocardial infarction. Finally, even though 94% of patients were successfully contacted for interviews, clinical outcomes may have been missed by this follow-up mechanism.

Nevertheless, the findings suggest that an abnormal TnT serum level in the perioperative period may be a useful predictor for major cardiac outcomes during the subsequent 6 months. This association may be due to a greater sensitivity for perioperative cardiac injury than is possible with CK-MB. These data indicate that elevated TnT levels in patients without clinical evidence for ischemia should not be dismissed as false positive results and that these patients may warrant further cardiac evaluation.

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